IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hsuan-Yin Lan-Hargest, et al. Art Unit : 1645
Serial No. : 09/812,945 Examiner : Bahar
Filed : March 27, 2001
Title : HISTONE DEACETYLASE INHIBITORS

BOX AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Appellants are appealing the final rejection of claims 1-53 dated April 23, 2002. A Notice of Appeal was filed on October 23, 2002. Appellants request that the rejection of these claims be reversed.

(1) Real Party in Interest

The real party of interest is CircaGen Pharmaceutical of Phoenix, Maryland, the assignee of the above-captioned application.

(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

Claims 1-53 are pending. Claims 3, 8, 9, 11, 13-16, 19-39, and 47-53 have been withdrawn from consideration. The claims being appealed are claims 1, 2, 4-7, 10, 12, 17, 18, and 40-46. Claim 1 is in independent form. A copy of the appealed claims as they presently stand is included as Appendix A.

(4) Status of Amendments

One amendment was filed subsequent to final rejection, canceling claims 54-66 without prejudice. The amendment filed subsequent to final rejection was entered.

(5) Summary of Invention

Histone deacetylase is a metallo-enzyme with zinc at the active site. Applicants have discovered a method of inhibiting histone deacetylase activity in cells. The method includes contacting the cells with an effective amount of a compound and determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions. *See* independent claim 1.

(6) Issues

(1) Whether the examiner erred in rejecting claims 1, 2, 4-7, 10, 12, 17-18, and 40-46 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

(2) Whether the examiner erred in rejecting claims 1, 2, 4-7, 10, 12, 17-18, and 40-46 under 35 U.S.C. §103(a) as being unpatentable over Richon *et al.*, *Proc. Nat. Acad. Sci.* 95(6):3003-7 (1999) ("Richon"), and Marks *et al.*, *J. Nat. Cancer Inst.* 92(5):1210-6 (2000) ("Marks").

(7) Grouping of Claims

Claims 1, 2, 4-7, 10, 12, 17, 18, and 40-46 are grouped together for the purposes of this appeal.

(8) Argument

Issue 1: Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-7, 10, 12, 17, 18, and 40-46 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Examiner contends that

> . . . the specification, while being enabling for some types of cancer, does not reasonably provide enablement for "treating cancer" in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Given the current state of the art, the treatment of all cancers broadly is unpredictable. One of ordinary skill in the art would not believe that one compound could treat all types of cancer with a single therapeutic agent. . . .

> . . . . The Skilled Artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen.

Office Action mailed Feb. 23, 2002, at 2-3. The error in this rejection stems from an erroneous interpretation of the clause "thereby treating one or more disorders" of independent claim 1.

Claim 1 recites "contacting the cells with an effective amount of a compound of formula (I), thereby treating one or more disorders mediated by histone deacetylase." The "thereby" clause in claim 1 "merely states the result of the limitations in the claim" and, as a result, "adds nothing to the patentability or substance of the claim." *Texas Instruments Inc. v. United States Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed. Cir. 1993).

The treatment described in the "thereby" clause of claim 1 is the result of contacting cells with an effective amount of a compound of formula (I). The recitation of treatment as the result obtained by contacting cells with an effective amount of a compound of formula (I) does not change the scope of the invention otherwise defined by claim 1. The treatment of a disorder, and the identity of the disorder, is not the invention being claimed.

In addition, the fact that Applicants elected cancer as the disorder being treated does not limit the scope of claim 1. The Examiner required election of a species *for examination* in the Office Action mailed November 6, 2001. Such an election does not alter the scope of the claim presented for examination. *See* MPEP § 809.02.

Properly construed, the method of claim 1 requires at least two actions to occur:

(1) contacting the cells with an effective amount of a compound of formula (I), and

(2) determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions.

The steps of contacting the cells with an effective amount of a compound of formula (I), and determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions are clearly enabled by the specification.[1] Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

---

[1] Applicants do not concede that the specification does not enable treatment of cancer in cells, but that is not what is claimed in the present application.

Issue 2: Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 4-7, 10, 12, 17, 18, and 40-46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Richon and Marks.

Richon describes the compounds suberoylanilide hydroxamic acid (SAHA) and m-carboxycinnamic acid bishydroxamide (CBHA). Those compounds are not included in the compounds recited in claim 1.

Marks describes histone deacetylase inhibitors. None of the compounds disclosed in Marks are included in claim 1.

The Examiner cited Richon and Marks as follows:

> Richon et al. teaches that hydroxamic acid derivatives, a class of hybrid bipolar compounds (HPCs) induce terminal differentiation and or apoptosis in various transformed cells, see abstract.
>
> Marks et al. teaches that hydroxamic acid-based HPCs are potentially effective agents for cancer therapy.
>
> Richon et al. and Marks et al. do not explicitly teach the elected compound in their method of treating cancer.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the elected compound in a method of treating cancer.
>
> One of ordinary skill in the art would have been motivated to employ the elected compound in a method of treating cancer because the elected compound is a hydroxamic acid derivative. The Skilled Artisan would reasonably expect the elected compound, a derivative of hydroxamic acid to exhibit therapeutic effects similar to hydroxamic acid because structurally related compounds would have been expected to have similar therapeutic effects.

Office Action mailed April 23, 2002, at 3-4 (citation omitted). The error in this rejection is that a *prima facie* case of obviousness has not been established. Specifically, Richon and Marks, whether considered individually or in combination, do not describe or suggest a method of inhibiting histone deacetylase activity in cells comprising the steps of "contacting the cells with an effective amount of a compound of formula (I)" and "determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions."

There are several structural differences between the SAHA and CBHA compounds disclosed in Richon and compounds of formula (I). To begin with, SAHA and CBHA do not fall

within the scope of formula (I). Furthermore, both SAHA (N-phenyl-N'-hydroxy-bisamide) and CBHA (N,N'-dihydroxy-bisamide) are "derivatives" of bis-amide. One would have to perform significant structural modifications of SAHA and CBHA in order to arrive at compounds of formula (I).

As with Richon, there are numerous structural differences between the histone deacetylase inhibitors disclosed in Marks and compounds of formula (I). Again, not only are the compounds disclosed in Marks not included within the scope of formula (I), one would have to perform significant structural modifications of those compounds in order to arrive at compounds of formula (I).

A significant error in the Examiner's rejection is that neither Richon nor Marks provide any suggestion or motivation to modify any of the compounds disclosed in those references.

> In determining whether a case of prima facie obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification. *The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.*

In re Lalu, 747 F.2d 703, 705 (Fed. Cir. 1984) (emphasis added); *see also In re Grabiak* ("[I]n the case before us there must be adequate support in the prior art for the ester/thioester change in structure, in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant.").

Taken either together or separately, Marks and Richon simply do not suggest to one of ordinary skill in the art to modify the compounds disclosed in those references at all, much less suggest the significant structural changes that would required to arrive at compounds of formula (I). In the absence of such suggestion, there is inadequate support for the Examiner's position that such a modification would be obvious.

The Examiner contends that "both references indicate that the anti-cancer activity as well as the HDAC inhibitory activity of hydroxamic acid compounds are known." Office Action mailed on April 23, 2002, at 4. This statement does not address Applicants' position that neither Marks nor Richon suggest any modifications of the compounds disclosed in those references.

The Examiner also contends that "Marks et al. provides a guide in choosing hydroxamic acid derivatives that have . . . 'a polar site, the hydroxamic group, a six-carbon hydrophobic methylene spacer, a second polar site and a terminal hydrophobic group.'" Office Action mailed on April 23, 2002, at 4-5 (citation omitted). Again, Marks does not suggest any modifications of the compounds disclosed in that reference. The general features quoted from Marks by the Examiner do not describe or suggest compounds of formula (I). In particular, Marks does not describe or suggest the groups identified as A, Y^1, L, Y^2, X^1 and X^2 in formula (I).

As discussed above, there is no motivation to modify the compounds disclosed in Richon and Marks so as to arrive at compounds of formula (I). In addition, neither reference describes or suggests using compounds of formula (I) *in the method of claim 1*. Specifically, neither Richon nor Marks, whether considered together or separately, describes or suggests contacting cells with an effective amount of a compound of formula (I) and determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions.

Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Claim 1, and claims that depend from claim 1 are patentable over Marks and Richon. Applicants therefore respectfully requests reconsideration and withdrawal of the rejection of under 35 U.S.C. §103(a) over Richon and Marks.

Conclusion

The rejection of all claims should be reversed for the reasons given above. The brief fee of $160 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

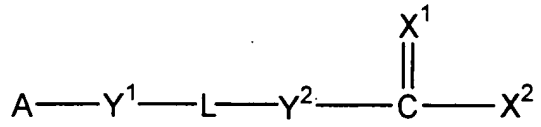
Date: 12-23-02

Harold H. Fox
Reg. No. 41,498

Fish & Richardson P.C.
1425 K Street, N.W.
11th Floor
Washington, DC 20005-3500
Telephone: (202) 783-5070
Facsimile: (202) 783-2331
40135335.doc

Appendix of Claims

1. A method of inhibiting histone deacetylation activity in cells comprising contacting the cells with an effective amount of a compound of formula (I), thereby treating one or more disorders mediated by histone deacetylase; said compound having the following formula:



(I)

wherein

A is a cyclic moiety selected from the group consisting of C_{3-14} cycloalkyl, 3-14 membered heterocycloalkyl, C_{4-14} cycloalkenyl, 3-8 membered heterocycloalkenyl, aryl, or heteroaryl; the cyclic moiety being optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylsulfonylamino, aminosulfonyl, or alkylsulfonyl; or A is a saturated branched C_{3-12} hydrocarbon chain or an unsaturated branched C_{3-12} hydrocarbon chain optionally interrupted by -O-, -S-, -N(R^a)-, -C(O)-, -N(R^a)-SO_2-, -SO_2-N(R^a)-, -N(R^a)-C(O)-O-, -O-C(O)-N(R^a)-, -N(R^a)-C(O)-N(R^b)-, -O-C(O)-, -C(O)-O-, -O-SO_2-, -SO_2-O-, or -O-C(O)-O-, where each of R^a and R^b, independently, is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl; each of the saturated and the unsaturated branched hydrocarbon chain being optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylsulfonylamino, aminosulfonyl, or alkylsulfonyl;

each of Y^1 and Y^2, independently, is -CH_2-, -O-, -S-, -N(R^c)-, -N(R^c)-C(O)-O-, -O-C(O)-N(R^c)-, -N(R^c)-C(O)-N(R^d)-, -O-C(O)-O-, or a bond; each of R^c and R^d, independently, being hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl;

L is a straight C_{2-12} hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxyl,

halo, amino, nitro, cyano, C_{3-5} cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyl, or formyl; and further being optionally interrupted by -O-, -N(R^e)-, -N(R^e)-C(O)-O-, -O-C(O)-N(R^e)-, -N(R^e)-C(O)-N(R^f)-, or -O-C(O)-O-; each of R^e and R^f, independently, being hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl;

X^1 is O or S; and

X^2 is -OR^1, -SR^1, -NR^3-OR^1, -NR^3-SR^1, -C(O)-OR^1, -CHR^4-OR^1, -N=N-C(O)-$N(R^3)_2$, or -O-CHR^4-O-C(O)-R^5, where each of R^1 and R^2, independently, is hydrogen, alkyl, hydroxylalkyl, haloalkyl, or a hydroxyl protecting group; R^3 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, haloalkyl, or an amino protecting group; R^4 is hydrogen, alkyl, hydroxylalkyl, or haloalkyl; R^5 is alkyl, hydroxylalkyl, or haloalkyl; and provided that when L is a C_{2-3} hydrocarbon containing no double bonds and X^2 is -OR^1, Y^1 is not a bond and Y^2 is not a bond;

or a salt thereof; and

determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions.

2. The method of claim 1, wherein X^1 is O.

4. The method of claim 1, wherein X^2 is -OR^1, -NR^3-OR^1, -C(O)-OR^1, -CHR^4-OR^1, or -O-CHR^4-O-C(O)-R^5.

5. The method of claim 1, wherein X^2 is -OR^1, -NR^3-OR^1, -C(O)OR^1, or -O-CHR^4-O-C(O)-R^5.

6. The method of claim 1, wherein each of Y^1 and Y^2, independently, is -CH_2-, -O-, -N(R^c)-, or a bond.

7. The method of claim 1, wherein each of Y^1 and Y^2, independently, is $-CH_2-$ or a bond.

10. The method of claim 1, wherein L is an unsaturated hydrocarbon chain containing at least one double bond and no triple bond.

12. The method of claim 10, wherein the double bond is in trans configuration.

17. The method of claim 1, wherein A is phenyl, naphthyl, indanyl, or tetrahydronaphthyl.

18. The method of claim 1, wherein A is phenyl optionally substituted with alkyl alkenyl, alkynyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, or amino.

40. The method of claim 1, wherein said compound is 5-phenyl-2,4-pentadienoic acid, 3-methyl-5-phenyl-2,4-pentadienoic acid, 4-methyl-5-phenyl-2,4-pentadienoic acid, 4-chloro-5-phenyl-2,4-pentadienoic acid, 5-(4-dimethylaminophenyl)-2,4-pentadienoic acid, 5-(2-furyl)-2,4-pentadienoic acid, 5-phenyl-2-en-4-yn-pentanoic acid, 6-phenyl-3,5-hexadienoic acid, 7-phenyl-2,4,6-heptatrienoic acid, 8-phenyl-3,5,7-octatrienoic acid, potassium 2-oxo-6-phenyl-3,5-hexadienoate, potassium 2-oxo-8-phenyl-3,5,7-octatrienoate, cinnamoylhydroxamic acid, methyl-cinnamoylhydroxamic acid, 4-cyclohexanebutyroylhydroxamic acid, benzylthioglycoloylhydroxamic acid, 5-phenylpentanoylhydroxamic acid, 5-phenyl-2,4-pentadienoylhydroxamic acid, N-methyl-5-phenyl-2,4-pentadienoylhydroxamic acid, 3-methyl-5-phenyl-2,4-pentadienoylhydroxamic acid, 4-methyl-5-phenyl-2,4-pentadienoyl hydroxamic acid, 4-chloro-5-phenyl-2,4-pentadienoylhydroxamic acid, 5-(4-dimethylaminophenyl)-2,4-pentadienoylhydroxamic acid, 5-phenyl-2-en-4-yn-pentanoylhydroxamic acid, 5-(2-furyl)-2,4-pentadienoylhydroxamic acid, 6-phenylhexanoylhydroxamic acid, 6-phenyl-3,5-hexadienoylhydroxamic acid, N-methyl-6-phenyl-3,5-hexadienoylhydroxamic acid, 7-phenylheptanoylhydroxamic acid, 7-phenyl-2,4,6-hepta-trienoylhydroxamic acid or 8-phenyloctanoylhydroxamic acid.

41. The method of claim 1, wherein said compound is 5-phenyl-2,4-pentadienoic acid, 8-phenyl-3,5,7-octatrienoic acid, potassium 2-oxo-8-phenyl-3,5,7-octatrienoate, benzylthioglycoloylhydroxamic acid, 5-phenyl-2,4-pentadienoylhydroxamic acid, 6-phenylhexanoylhydroxamic acid, 7-phenyl-2,4,6-hepta-trienoylhydroxamic acid, or 8-phenyloctanoylhydroxamic acid.

42. The method of claim 1, wherein the cells are treated with a compound of formula (I) in vivo.

43. The method of claim 1, wherein the cells are treated with a compound of formula (I) in vitro.

44. The method of claim 1, wherein the cells being treated are cancerous.

45. The method of claim 1, wherein the disorder is selected from the group consisting of cancer, hemoglobinopathies, thalassemia, sickle cell anemia, cystic fibrosis, protozoan infection, adrenoleukodystrophy, alpha-1 anti-trypsin, retrovirus gene vector reactivation, wound healing, hair growth, peroxisome biogenesis disorder, and adrenoleukodystrophy.

46. The method of claim 1, wherein the disorder is cancer, cystic fibrosis, or adrenoleukodystrophy.